Review
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Immune checkpoint blockade for cancer therapy: current progress and perspectives

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Abstract: The dysfunction of anti-tumor immune responses is crucial for cancer progression. Immune checkpoint blockade (ICB), which could potentiate T cell responses, is an effective strategy for the normalization of host anti-tumor immunity. In recent years, immune checkpoints, expressed on both tumor cells and immune cells, have been identified; some of them have exhibited potential druggability and have been approved by the Food and Drug Administration (FDA) for clinical treatments. However, the limited responses and immune-related adverse events (irAEs) cannot be ignored. This review outlines the development and applications of ICBs, potential strategies for overcoming resistance, and future directions for ICB-based cancer immunotherapy.

Key words: Immune checkpoint blockade; Cancer immunotherapy; Tumor immune evasion; Immune normalization

1 Introduction

Over the past century, cancer treatments have evolved from surgery, radiotherapy, and chemotherapy to the exciting realm of immunotherapy. Novel treatments keep pace with a deeper understanding of the immune response against tumors. At present, the main approaches to cancer immunotherapies include general immune stimulation, vaccination, immune checkpoint blockade (ICB), and adoptive T cell transfers (Li et al., 2019). The conventional strategies of cancer immunotherapy comprise harnessing immune effector cells and molecules to kill tumor cells directly, or modulating intrinsic immune mechanisms to attack tumor cells indirectly (Sanmamed and Chen, 2018). However, “immune enhancement” strategies usually lead to non-negligible

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immune-related adverse events (irAEs). Nowadays, there is a shift towards normalization strategies, aiming to restore particular dysfunctional immune responses that tumor cells employed for immune evasion (Dunn et al., 2002; Sanmamed and Chen, 2018).

Immune checkpoints are a collection of multiple inhibitory pathways balanced with co-stimulatory receptor activity to restrain T cell activation (Pardoll, 2012; Andrews et al., 2017). Continuous exposure to tumor antigens during cancer results in the rewriting of immune checkpoints on antigen-specific T cells, causing effector T cell unresponsiveness or exhaustion (Virgin et al., 2009; Zarour, 2016), a predominant mechanism mediating tumor immune escape. ICBs block immune checkpoints and function to reverse the immune tolerance, which fulfils the normal anti-tumor immune responses of T cells. Additionally, antigen-presenting cells (APCs) of the myeloid lineage and myeloid cells in the tumor microenvironment (TME) also play an important role in modulating immune responses to cancer. Thus, the immune checkpoints of myeloid cells have also been developed (Park and Kim, 2019).

This review provides insights into the basic mechanisms of ICBs and recent clinical trials targeting immune checkpoints on T cells and myeloid cells. Additionally, it explores the mechanisms and strategies for overcoming immunotherapy resistance, offering perspectives for future immunotherapy developments.

2 Blockade of T cell-based Immune Checkpoints

2.1 Cytotoxic T Lymphocyte Antigen-4

T cell activation requires a major histocompatibility complex (MHC)/antigen- T cell receptor (TCR) signal alongside a co-stimulatory signal (Chen and Flies, 2013). CD28 is constitutively expressed on the cell surface of naive T cells, and provides a co-stimulatory signal for T cell activation upon ligation by B7-1 (CD80) or B7-2 (CD86) on APCs (Sansom, 2000). Cytotoxic T Lymphocyte Antigen-4 (CTLA4), also known as CD152, is a global checkpoint molecule induced following T cell activation (Rudd et al., 2009). As a homologous protein of CD28, CTLA4 competes with CD28 on T cells for binding to the same ligands with a much higher binding affinity, therefore blocking T cell response (Rudd, et al., 2009). Thus, CTLA-4 critically contributes to a dysfunction of T cell activation. In the tumor microenvironment, CTLA4 mainly leads to the repression of CD4+ T cells priming and the induction of regulatory T cell (Tregs) activity (Linsley et al., 1996; Topalian et al., 2016).

A fully-humanized CTLA-4 IgG1 monoclonal antibody (mAb), ipilimumab (Yervoy), was the first T cell-targeting antibody approved by the Food and Drug Administration (FDA) in 2011 for patients with advanced melanoma to enhance anti-tumor immune response (Ribas and Wolchok, 2018). Besides melanoma, the FDA also approved ipilimumab to treat advanced renal cell carcinoma (RCC) and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer combined with nivolumab (anti-PD-1) (Rotte, 2019). There are approximately 834 clinical trials of ipilimumab in patients with lung cancer,

gastrointestinal (GI) cancer, prostate cancer, and many other cancer types. It has been shown that ipilimumab can mediate objective tumor regression in nearly 15% of patients with metastatic melanoma and significantly improved median overall survival (OS) (Attia et al., 2005; Downey et al., 2007; Hodi et al., 2010). Meanwhile, in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the usage of ipilimumab is associated with improved OS and progression-free survival (PFS) compared with non-ipilimumab therapies (Xu et al., 2022).

However, ipilimumab treatment poses challenges due to the frequency of irAEs, which is correlated with dosage (Wolchok et al., 2010). Therefore, ipilimumab is limited at the FDA-approved dose of 3 mg/kg to treat patients with melanoma. With the treatment of ipilimumab, irAEs occurred in nearly 60% of patients with unresectable stage III or IV melanoma. Although a large proportion of irAEs can be relieved by steroid administration (Weber et al., 2012), identifying predictive biomarkers, such as TME genes, tumor mutation burden (TMB), GI-irAEs, and CD39+ tumor-resident cytotoxic T cells, is crucial for determining the potential benefit for patients and guiding personalized ipilimumab therapies (Abu-Sbeih et al., 2019; Krijgsman et al., 2021; Attrill et al., 2022).

2.2 Programmed cell death 1

PD-1, or CD279, discovered by Tasuku Honjo in 1992, is initially associated with apoptosis (Ishida et al., 1992). PD-1 engagement with its ligands, programmed death-ligand 1 (PD-L1, also known as CD274, B7H1) and PD-L2 (also known as B7-DC, CD273), transmits the co-inhibitory signaling into the cell to constrain proliferation and cytokine production (Keir et al., 2008). In various human carcinomas, including lung cancer, ovarian cancer, colorectal cancer, and melanomas, PD-L1 and PD-L2 are broadly expressed on the surface of B cells, DCs, macrophages, bone marrow (BM)-derived mast cells, and T cells (Dong et al., 2002; Francisco et al., 2010). The targeting PD-1 and/or PD-L1 is a promising option for tumor treatment. On average, 25% of patients with solid tumors and 40–60% of patients with lymphomas earned benefits from anti-PD-1/PD-L1 therapy (Kim et al., 2022). Until now, the FDA has approved seven antibodies targeting PD-1/PD-L1, and we counted the number of clinical trials on these approved immune checkpoint inhibitors (ICIs), respectively (Table 1)

The objective response rate (ORR) diverges from types of cancer, with an ORR of 40.0% to nivolumab in previously untreated advanced melanoma (Robert et al., 2015) and of 11.6% in recurrent SCLC (Ready et al., 2020). Given the unstable efficacy between patients, the high costs, and severe irAEs, it is important to distinguish responders from non-responders by utilizing new biomarkers. High tumor mutational burden, microsatellite instability, and tumor PD-L1 expression were approved for diagnostic tests in clinical trials (Le et al., 2015; Reck et al., 2016; Yarchoan et al., 2017; Li et al., 2022). Furthermore, inflammatory tumor microenvironment signatures, human leukocyte antigen (HLA) heterozygosity, and mutations are potential biomarkers for predicting responders, supported by cumulated evidence (Chowell et al., 2018; Higgs et al., 2018). Additionally, intra-tumoral plasma cells can predict the OS of NSCLC patients treated with atezolizumab (Patil et al., 2022).

High levels of CD8+ tumor-infiltrating cells expressing PD-1 but not T cell immunoglobulin and mucin-domain containing-3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3) correlate to a better response to nivolumab versus everolimus (an mTOR inhibitor) in patients with metastatic clear cell renal cell carcinoma (mccRCC) (Ficial et al., 2021). Moreover, 89Zr-pembrolizumab PET imaging can serve as a non-invasive approach with which to assess the clinical response to PD-1 blockade (Kok et al., 2022).

Restricted by the low response rate, anti-PD-1/PD-L1 therapy turns to combination strategies. One study integrating 4897 active trials for anti-PD-1/PD-L1 therapy reveals that 4062 (83%) trials are combined with chemotherapies, radiotherapies, targeted therapies, and Immuno-Oncology (I-O) therapies. Among them, the VEGF/VEGFR-targeted therapy, chemotherapy, and CTLA-4 antibodies are the most prominent combination strategies (Upadhaya et al., 2022). In particular, nivolumab plus ipilimumab (anti-CTLA-4) is approved by the FDA for melanoma, NSCLC, RCC, hepatocellular carcinoma (HCC), and colorectal cancer (CRC). This combination showed ameliorated PFS and median OS compared to monotherapy (Wolchok et al., 2022), although accompanied by a higher rate of irAEs (Geraud et al., 2021). Tumor-associated high endothelial venules (TA-HEVs) can be used to predict the response to and survival of the treatment with PD-1 and CTLA-4 blockade (Asrir et al., 2022). Additionally, in a phase II clinical trial, ramucirumab (a monoclonal antibody that targeted VEGFR2) plus pembrolizumab resulted in a longer OS compared with standard-of-care (SOC) in advanced NSCLC (Reckamp et al., 2022). Recently, a study has proven that the combination of CXCR4-targeted p53 mRNA nanoparticles and PD-1 blockade can suppress cancer cell growth by increasing the number of immune cells such as activated CD8+T cells and mature NK cells, and by raising the level of TNF- , IL-2, and IL-1 in HCC (Xiao et al., 2022). However, some positive preclinical results fail to be replicated in the clinic and in combination therapy with an amplified risk of irAEs. Thus, understanding tumor-induced adaptive immune resistance (AIR) and irAEs is crucial for guiding future immunotherapy. Therefore, we include Table 2 to show the incidence of some common all-grade potential irAEs in advanced melanoma after the use of some specific ICIs.

2.3 B7 homolog 3

B7 homolog 3 (B7-H3) (also known as CD276), a member of the B7-CD28 pathway family (Chapoval et al., 2001), is widely expressed on non-hematopoietic cells, including cancer cells (Lines et al., 2014b), and can be induced on some immune cells (Lines et al., 2014a). B7-H3 is overexpressed in many kinds of cancers, and is involved in proliferation, migration, and invasion in cancer developments. Notably, it was found that the soluble form of B7-H3 is an effective biomarker for poor prognosis in patients with NSCLC, which is even better than traditional biomarkers such as carcinoembryonic antigen (CEA) (Lines, et al., 2014b).

There are more than 20 clinical trials of B7-H3-targeting mAb-based immune checkpoint therapies. Different immunotherapeutic strategies have been used to target B7-H3. The first is B7-H3-targeting radioimmunotherapy; 8H9 (omburtamab), a mAb specific to B7-H3, is radiolabeled to iodine-131 (^{131}I) for patients

with neuroblastoma, peritoneal cancers, advanced central nervous system tumors, or leptomeningeal cancer in clinical trials (Janakiram et al., 2017). It is well-tolerated without dose-limiting toxicities (DLTs) and has low radiation exposure to normal organs in patients with B7-H3-expressing tumors (Modak et al., 2020). Another B7-H3 targeting strategy is the novel Fc-enhanced mAbs, such as enoblituzumab (MGA271), an IgG1 mAb against B7-H3 with potent anti-tumor activity through antibody-dependent cell-mediated cytotoxicity (ADCC) (Janakiram, et al., 2017). Enoblituzumab has been investigated in prostate cancer, NSCLC, melanoma, and other refractory cancers, and has produced results with good tolerance (Picarda et al., 2016). However, its combination with pembrolizumab (anti-PD-1) showed potential in metastatic NSCLC and recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) along with irAEs, including infusion-related reactions (IRRs) and fatigue (Aggarwal et al., 2022). Other categories include antibody–drug conjugates (ADCs): trials on MGC018, CD3-engaging bispecific antibodies (BsAbs): obrindatamab (MGD009), and tri-specific killer engagers (TriKEs) are all ongoing to assess their efficacy (Kontos et al., 2021). The irAEs of these strategies still need further studies.

2.4 B7 homolog 4

B7 homolog 4 (B7-H4), another member of the B7 family, is also known as B7x, a V-set domain-containing T cell activation inhibitor 1 (VTCN1) or B7S1 (Choi et al., 2003). Its mRNA is detectable on most non-hematopoietic tissues, but the expression of protein is limited in APCs and cancer cells such as NSCLC, melanoma, stomach, prostate, and breast cancers, which can be induced by IL-6 and IL-10 (Ceeraz et al., 2013; Li et al., 2018). Its receptor is assumed to be the B and T lymphocyte attenuator (BTLA) (Watanabe et al., 2003). B7-H4 expression was especially confirmed to be associated with cancer cell stemness in prostate cancer (Li et al., 2020b). The silence of B7-H4 expression in CRC can reduce the viability and migration of cells and inhibit epithelial–mesenchymal transition (EMT) process (Li et al., 2020a; Yin et al., 2022).

FPA150 is the first B7-H4 antibody tested in an early phase I trial in combination with pembrolizumab (anti-PD-1) for patients with breast cancer, ovarian cancer, and endometrial cancer to evaluate its dosing, safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy (Andrews et al., 2019). It appeared to be well tolerated, with grade 1-2 TRAEs, including 16.7% diarrhea and 13.8% fatigue (Wainberg et al., 2019). NC762, another B7-H4-targeting mAb, is still under clinical trials for ovarian cancer, NSCLC, and breast cancer. Additionally, B7-H4 and CD3-bispecific mAbs such as PF-07260437 and GEN1047 are being tested in breast cancer, ovarian cancer, and some other advanced or metastatic solid tumors to evaluate their safety and tolerability to determine the recommended dose.

2.5 V-domain Ig suppressor of T-cell activation

A new target for cancer immunotherapy is the Ig superfamily member V-domain Ig suppressor of T cell activation (VISTA), also named B7-H5, PD1 homolog (PD-1H), differentiation of ESC-1 (Dies1), C10orf54,

stress induced secreted protein 1 (SISP1), or platelet receptor Gi24 precursor (Wang et al., 2011; Huang et al., 2020). VISTA is mainly expressed on hematopoietic cells, with the highest level observed in leukocytes and myeloid cells (Lines, et al., 2014a; Wu et al., 2021). In addition, VISTA is implicated in various kinds of cancers, such as melanoma, NSCLC, pancreatic cancer, and prostate cancer (Huang, et al., 2020). Endogenous VISTA has immuno-inhibitory effects both as a ligand on APCs and as a receptor on T cells (Flies et al., 2014). Some studies showed that v-set and immunoglobulin domain-containing 3 (VSIG-3)/ immunoglobulin superfamily 11 (IgSF11) is the ligand of VISTA, which contributes to the suppression of T cell responses in vitro by enhancing IL-2, IL-17, and interferon-γ (IFN-γ) production (Wang et al., 2019). Importantly, as an acidic pH-selective ligand for P-selectin glycoprotein ligand-1 (PSGL-1), VISTA specifically mediates immune suppression in the acidic tumor microenvironment (Johnston et al., 2019).

CA-170, an oral checkpoint antagonist for VISTA, has been confirmed to interfere with the suppression of T cell activation and cytokine production by VISTA (Musielak et al., 2019). The potential pharmacologically active dose of tumors expressing VISTA has been evaluated in a phase I clinical trial in lymphomas, mesothelioma, NSCLC, and triple negative breast cancer. CA-170 was found to induce grade 1-2 TRAEs, including fever, fatigue, chills, and nausea. Another phase II trial treated patients with non-squamous NSCLC with 400mg CA-170, which showed superior efficacy, with a clinical benefit rate (CBR) of 75% and median PFS of 19.5 weeks (Radhakrishnan et al., 2019). The safety of JNJ-61610588, an IgG1 anti-VISTA mAb, was investigated in a phase I trial in treating patients with advanced cancer such as metastatic NSCLC. However, it was terminated due to the obvious side effect (Eltanbouly et al., 2020).

2.6 T cell immunoglobulin domain and mucin-domain containing-3

TIM-3, a member of the TIM family, was first discovered in 2002 and is considered a cell surface marker of Th1 (Monney et al., 2002). Among the TIM family, due to the negative effects on Th1 responses and the production of proinflammatory cytokines, such as TNF and IFN-γ (Das et al., 2017)**,** TIM-3 attracts the most attention. TIM-3 is expressed on (IFN-γ)-producing T cells, Tregs, myeloid cells, NK cells, and mast cells (Wolf et al., 2020). It plays an inhibitory role through binding to different ligands, including galectin 9, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), phosphatidylserine (PtdSer), and high mobility group box 1 (HMGB1) (Zhu et al., 2005; Chiba et al., 2012; Huang et al., 2015). The absence of TIM-3 activates inflammasome to promote anti-tumor immunity (Dixon et al., 2021). TIM-3 is also expressed in many types of cancers, such as melanoma and NSCLC, with a trend to poor clinical prognosis (Fourcade et al., 2010; Gao et al., 2012). Moreover, TIM-3 blockade can reduce the PI3K/AKT/mTOR signaling-mediated inhibition of NK cells in HCC (Tan et al., 2020), underscoring its significance in the immunotherapy of cancer patients.

Mechanistic insights into the inhibitory function of TIM-3 and potential therapeutic evidence of TIM-3 blockade in combination with anti-PD1 therapy boost the development of anti-TIM-3 blocking antibodies. The first trial data are about TSR-022 (cobolimab), a humanized anti-TIM-3 IgG4 antibody designed by Tesaro

(Murtaza et al., 2016). The combination treatment of TSR-022 and anti-PD1 antibody dostarlimab (TSR-042) is proven to increase clinical activity in patients with NSCLC that do not respond to anti-PD1 or anti-PD-L1 treatments (Davar et al., 2018). The TIM-3 blocking antibodies, LY3321367 of Eli Lilly (Harding et al., 2019) and MGB453 (sabatolimab) of Novartis (Ahn, 2018), have both completed a phase I clinical trial. LY3321367 is reported to lead to TRAEs including diarrhea, pruritus, fatigue, and anorexia without DLTs (Harding et al., 2021). The combination of LY3321367 with LY3300054 (anti-PD-L1 antibody) did not change the frequencies and types of TRAEs compared with LY3300054 monotherapy, but led to higher response rates (Hollebecque et al., 2021). Now dual targeting of TIM-3 and PD-1 by RO7121611 has been trialed for metastatic solid tumors, NSCLS, and some other cancers (Gomes De Morais et al., 2022).

2.7 Lymphocyte-activation gene 3

LAG-3 is the third clinically targeted antagonistic mAb inhibitory receptor (IR) (Andrews, et al., 2017). LAG-3 is expressed on a subset of NK cells (Triebel et al., 1990), T cells (Triebel, et al., 1990), thymus-derived Tregs (Huang et al., 2004), plasmacytoid DCs in mice (Workman et al., 2009), invariant NKT cells, and B cells (Workman et al., 2002; Kisielow et al., 2005). In effector T cells, the crosslinking of LAG-3 and CD3/TCR complex suppresses TCR-induced T cell proliferation, cytokine production, and calcium flux (Hannier et al., 1998). LAG-3 plays an essential role in T cell homeostasis by directly suppressing T cells or indirectly inhibiting Tregs (Workman and Vignali, 2005).

There are over 20 antibodies targeting LAG-3, including soluble LAG-3-Ig fusion protein (IMP321), monoclonal antibodies (relatlimab, sym022, TSR-033, REGN3767, LAG525), and bispecific antibodies (MGD013, FD118, XmAb22841). In a phase 1/2 study of LAG525 and anti-PD-1 spartalizumab (PDR001), the frequencies of TRAEs are 56% and 69% in the LAG525 monotherapy and the combination strategy, respectively. TRAEs commonly had low severity, such as fatigue, gastrointestinal, and dermatosis (Schöffski et al., 2022). In a phase 2-3 clinical trial, relatlimab plus nivolumab (anti-PD-1) significantly improved the median PFS versus nivolumab alone (10.1 months vs. 4.6 months) in previously untreated metastatic or unresectable melanoma. Of the patients receiving combination arms, 18.9% had grade 3 or 4 TRAEs (Tawbi et al., 2022). Subsequently, in March 2022, nivolumab plus relatlimab gained approval from the FDA for the treatment of unresectable or metastatic melanoma.

2.8 T cell immunoglobulin and ITIM domain

TIGIT (T cell immunoglobulin and ITIM domain) is a surface protein that was identified in the human lymphocyte population as a member of the CD28 family in 2009 (Yu et al., 2009). TIGIT is expressed on activated T cells, NK cells, memory T cells, and a subset of Treg cells (Yu, et al., 2009). The ligands of TIGIT—CD155 (poliovirus receptor, PVR) and CD112 (PVRL2, nectin-2)—which are expressed on APCs, T cells, and a variety of non-hematopoietic cell types including tumor cells, play a tremendous role in mediating immune inhibitory functions (Mendelsohn et al., 1989; Casado et al., 2009; Stanietsky et al., 2009; Yu, et al., 2009;

Levin et al., 2011).

TIGIT features a cytoplasmic tail containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoglobulin tail tyrosine (ITT)-like motif, which are conserved between mice and humans. TIGIT leads to a strong reduction of NK cell functions via its ITT-like domain (Stanietsky, et al., 2009; Liu et al., 2013). The phosphorylated ITT-like domain binds to adaptor proteins, including Grb2 and β-arrestin 2, which further recruit SHIP1 to suppress NK cell function via PI3K/MAPK signaling or NF-κB signaling (Liu, et al., 2013; Li et al., 2014). For T cells, the activation of TIGIT negatively affects different facets of the functions of T cells, such as productive T cell activation and proliferation, and the acquisition of effector functions (Yu, et al., 2009; Joller et al., 2011). It targets the TCR signaling pathway, in which it downregulates the components of the TCR complex and PLCγ, the central regulator of the TCR signaling cascade (Joller, et al., 2011).

So far, there have been 75 clinical trials on TIGIT-related drugs; most of them are in phase I or phase II. Currently, there are four TIGIT monoclonal antibodies in phase III trials, including tiragolumab, ociperlimab, vibostolimab, and domvanalimab. For example, the anti-TIGIT antibody vibostolimab, as a monotherapy or in combination with pembrolizumab (anti-PD1), is in a first-in-human phase 1 study to cure patients with advanced solid tumors, including advanced NSCLC. TRAEs occurred in 62% of patients, and even 17% had grade 3-4 TRAEs. The most common TRAEs were pruritus (17%) and rash (14%) (Niu et al., 2021). Recently, a phase 1 trial of the combination of anti-TIGIT antibody etigilimab and nivolumab found a notably increased median PFS of 57.5 days (Mettu et al., 2022).

2.9 B and T lymphocyte attenuator

B and T lymphocyte attenuator (BTLA), a co-inhibitor which is also known as B and T lymphocyte-associated protein or CD antigen CD272, is an Ig domain superfamily protein with cytoplasmic ITIM and an immunoreceptor tyrosine-based switch motif (ITSM). Discovered in 2003, BTLA is widely expressed on many immune cells, such as Th1 cells, bone marrow-derived $CD11c^+$ DCs, resting peripheral B cells, anergic T cells, and T follicular helper (Tfh) cells (Watanabe, et al., 2003; Han et al., 2004; Hurchla et al., 2005; Loyet et al., 2005; Nurieva et al., 2008; M'hidi et al., 2009). BTLA was also found in NSCLS, and its expression was positively correlated with PD-L1 expression, which showed a synergistic action (Li et al., 2020d).

BTLA has some similarities with PD-1 and CTLA-4, for they are all Ig domain-containing inhibitory receptors (Watanabe, et al., 2003). However, BTLA is unique because its ligand, herpesvirus entry mediator (HVEM), is a TNFR superfamily member rather than an Ig domain-containing protein (Gonzalez et al., 2005; Sedy et al., 2005). The BTLA/HVEM signaling functions bidirectionally in T cell regulation. Concerning trans interaction, both ITIM and ITSM of BTLA can be phosphorylated and recruit Src homology 2 (SH2) domain-containing protein tyrosine phosphatase 1 and 2 (SHP1/2) to inhibit both TCR and CD28 signaling after interacting with the cysteine-rich domain 1 (CRD1) region of HVEM, thus suppressing T cell function (Gavrieli et al., 2003; Watanabe, et al., 2003; Sedy, et al., 2005). Additionally, the cis interaction between HVEM and

BTLA prevents HVEM from being activated by trans ligation and provides proinflammatory signals (Cheung et al., 2009).

Given the complexity of the BTLA/HVEM signaling pathway, whether or not the BTLA blockade can be used on immunotherapy seems to be a context-specific decision. It is reported that the BTLA/HVEM axis downregulated IFN-γ production and NK cell-mediated cytotoxicity to promote NK cell immunosuppression in chronic lymphocytic leukemia (CLL), and the BTLA blockade worked in reversing the effects (Sordo-Bahamonde et al., 2021). JS004 is the first anti-BTLA monoclonal antibody approved in clinical trials by the FDA, which intends to cure advanced unresectable or metastatic solid tumors (including lymphoma). In a phase I study of JS004 as a single agent or in combination with toripalimab (anti-PD1) in relapsed/refractory lymphomas, 83.3% of patients experienced treatment emergent adverse events (TEAEs), with 18.8% experiencing TEAEs of grade 3 or higher (Ma et al., 2022). miR-32 can inhibit the metastasis and proliferation of ovarian cancer cells as a suppressor gene by regulating the target gene BTLA (Zhang et al., 2020); still, no BTLA-targeted drug has yet been approved for tumor treatment by the FDA.

We summarize the clinical trials on current novel ICIs with corresponding phase and tumor types to give readers an intuitive sense of these ICIs (ClinicalTrials.gov) (Table 3).

3 Myeloid Immune Checkpoints

Knowledge about immune checkpoints expressed on myeloid cells has been expanding in recent years (Figure 1), and they have been proven to critically suppress anti-tumor immune responses in the TME (Nakayama et al., 2009; Yao et al., 2009; Bally et al., 2015).

The first class of myeloid immune checkpoint acts as a “negative regulator”, of which PD-1 and TIM-3 are the most representative due to their impressive immunosuppressive function on T cells. In macrophages, PD-1 expression is upregulated by Toll-like receptors (TLRs)-induced NF-κB activation (Bally, et al., 2015; Martinez et al., 2015; Voron et al., 2015). PD-1 expressed on DCs negatively regulates proinflammatory cytokine production (Yao, et al., 2009). TIM-3 expressed on DCs competitively binds to dying cell-derived HMGB1, which could activate innate immune responses through TLRs and RIG-I (Chiba, et al., 2012).

The second class of myeloid immune checkpoints has a great impact on the phagocytosis of myeloid cells, including monocytes, macrophages, and neutrophils. On recognizing the ligands on tumor cells, they can downregulate the clearing ability of myeloid cells. For instance, signal regulatory protein α (SIRPα) is a member of the SIRP-paired receptor family that has ITIMs. Upon the recognition of its ligand, CD47, SIRPα recruits SHP1/2, leading to the negative regulation of phagocytosis (Nakamura and Smyth, 2020). Another checkpoint is leukocyte immunoglobulin-like receptor (LILR), which belongs to the superfamily of paired receptors and can be divided into inhibitory LILRBs and activating LILRAs (Kuroki et al., 2012; Burshtyn and

Morcos, 2016). Inhibitory LILRB1 and LILRB2 are well characterized to recognize classic and non-classic MHC class-I (Held and Mariuzza, 2008). LILRBs might also transmit a “don’t eat me signal” in monocytes and macrophages. Blockade of LILRB1 unleashes tumor MHC class-I-induced negative regulation of phagocytosis (Barkal et al., 2018). It is noted that sialic-acid-binding Ig-like lectin 10 (Siglec-10), which is a family of sialic acid-binding immunoglobulin-like receptors expressed on B cells, monocytes, and eosinophils in humans, can downregulate inflammatory responses through the recruitment of SHP1/2 when interacting with its ligand, CD24 (Chen et al., 2009; Chen et al., 2011; Macauley et al., 2014).

The third class contains several scavenger receptors on macrophages, such as scavenger receptor-A (SR-A), macrophage receptor with collagenous structure (MARCO), and Clever-1 (common lymphatic endothelial and vascular endothelial receptor-1, also known as stabilin-1 or FEEL1) (Salmi et al., 2004; Arredouani et al., 2007). SR-A (also known as CD204) can recognize low-density lipoproteins (LDLs), heat shock proteins, proteoglycans, and various PAMPs. High expression levels of SR-A on tumor-associated macrophages (TAMs) correlate with tumor invasiveness and angiogenesis in patients with lung and esophagus squamous carcinoma (Hirayama et al., 2012; Shigeoka et al., 2013).

c-Rel, a member of the NF-κB family, acts as an intracellular checkpoint by selectively activating pro-tumoral genes and deactivating anti-tumoral genes through a c-Rel enhanceosome. This results in the generation of myeloid-derived suppressor cells (MDSCs). Studies have shown that c-Rel deficiency in myeloid cells significantly reduced cancer growth in mice. Similarly, pharmaceutical inhibition of c-Rel also had the same effect. This suggests that c-Rel is a myeloid checkpoint that can be targeted for cancer treatment (Li et al., 2020c).

Some clinical trials have been carried out on these myeloid immune checkpoints. For example, anti-CD47 mAb (Hu5F9-G4) in combination with anti-CD20 mAb (rituximab) was tested in patients with relapsed and refractory B cell lymphoma (Advani et al., 2018). However, because myeloid subsets feature a high turnover rate, functional compensation, heterogeneity, and plasticity, targeting these immune checkpoints will be a great challenge.

4 Secreted Immune Checkpoint

IL-18 is a member of the IL-1 cytokine family, which can promote the activity of effector T cells and NK cells to increase the production of IFN-γ, thus inhibiting the proliferation of tumors (Srivastava et al., 2013; Yasuda et al., 2019). However, its decoy receptor IL-18 binding protein (BP) can neutralize IL-18 with higher affinity than the IL-18 receptor to reduce the induction of IFN-γ and downregulate Th1 responses (Nakanishi et al., 2001). The studies also found that, after patients received treatment with recombinant human IL-18 (rhIL-18), IL-18 was neutralized by IL-18BP (Robertson et al., 2006; Robertson et al., 2008). Because IL-18BP

is prevalent in the TME and is often upregulated in tumors, it acts as a secreted checkpoint to be the barrier to IL-18 immunotherapy (Zhou et al., 2020). Decoy-resistant IL-18 (DR-18) is a variant created to avoid the inhibition of IL-18BP, but with full signaling capacity; it has been proven that DR-18 can drive potent tumor growth inhibition in mouse tumors, and can elicit NK cell responses in MHC class I deficient tumors. It may be a promising way to treat cold tumors, which are not sensitive to traditional immunotherapy, although its clinical safety and pleiotropy are still worthy of attention (Zhou, et al., 2020).

5 Limitation of ICBs Clinical Application

5.1 Factors influencing resistance to ICB

Most cancer patients with primary resistance to ICB cannot benefit from the therapy. Some people who initially respond to the tretament also obtain acquired resistance, and consequently have adverse outcomes (Sharma et al., 2017). The response to immune checkpoint therapy is influenced by both host-intrinsic and host-extrinsic factors. Host-intrinsic factors include tumor and tumor microenvironment, host genomics and epigenomics, systemic immunity, systemic factors, and microbiota. For host-extrinsic factors, environmental exposures, psychosocial factors, lifestyle, and microbial factors also have a significant impact on the patient's response to ICB. The interaction of these factors and the coevolution of cancer and anti-tumor immunity also impacts the therapy immensely (Morad et al., 2021). The IFN-γ pathway plays a key role in primary and acquired resistance in checkpoint blockade therapy. T cells produce IFN-γ once they recognize tumor antigens, which activates the Janus kinase (JAK)-signal transducers and activators of the transcription (STAT) pathway, and upregulates the downstream expression of chemokines, in particular CXCL9, CXCL10, and CXCL11, to attract T cell infiltration (Castro et al., 2018; Grasso et al., 2020). Cancer cells can mutate or silence the molecules involved in the IFN-γ pathway to mediate immune escape (Benci et al., 2016).

It can be seen that abnormal cellular transduction signals, including the WNT/β-catenin pathway, PI3K/AKT pathway, and MAPK pathway, may be the factors leading to immunotherapy resistance (Barrueto et al., 2020). The activation of the melanoma-intrinsic WNT/β-catenin pathway can produce immunosuppressive cytokines, such as IL-10, and exclude T cell infiltration (Spranger et al., 2015). In melanoma cells, the soluble WNT agonist WNT5A can activate β-catenin signaling in dendritic cells, which induces downstream target indoleamine 2,3-dioxygenase 1 (IDO1) to catalyze the conversion of trypto-phan into kynurenine. It promotes the development of Tregs cells and results in the inhibition of effector T cell activity (Holtzhausen et al., 2015). PI3K can phosphorylate the metabolite phosphatidylinositol 4,5-bisphosphate (PIP2) to PIP3. PIP3 acts as a second messenger and promotes AKT activation, thereby stimulating cell proliferation, inhibiting apoptosis, and promoting angiogenesis. However, the lipid phosphatase PTEN can dephosphorylate PIP3 and turn it back to PIP2, terminating the PI3K signaling pathway (Fresno Vara et al., 2004). Therefore, the

loss of the lipid phosphatase PTEN in cancer can activate the PI3K/AKT pathway, thus reducing melanoma autophagic activity to facilitate the resistance to T cell-mediated tumor apoptosis (Peng et al., 2016). Ras can activate the Ras-Raf-MEK-ERK/MAPK phosphorylation cascade to regulate cell proliferation, survival, differentiation, and angiogenesis. Activating mutations of BRAF are common in different kinds of tumors, augmenting the expression of IL-6, IL-10, and VEGF to perform immunosuppressive functions (Sumimoto et al., 2006). In addition, a lack of neoantigens and the loss of antigen presentation can lead to the absence of tumor cell recognition, contributing to immunotherapy resistance (Barrueto, et al., 2020). Meanwhile, the specialized components of the TME, such as MDSCs, Tregs, and exhausted T cells, are also associated with ICB resistance (Kalbasi and Ribas, 2020). Hyper-progressive disease (HPD), a phenomenon of accelerated tumor growth after the administration of checkpoint inhibitors, occurs with an incidence from 4% to 29% (Borcoman et al., 2019), which will reduce survival durations (Champiat et al., 2017). However, the mechanism and predictive biomarkers of this phenomenon have not been well identified.

Genetic and epigenetic influences are significant factors impacting the response to ICB. Tumor cells can reduce HLA class I on their surface, thus influencing antigen presentation to escape immune recognition. Genetically, HLA loss of heterozygosity (LOH) or antigen-presentation machinery (APM) mutations can hinder antigen presentation (Rosenthal et al., 2019). The loss of beta-2 microglobulin (B2M) alleles, a component of HLA-I that maintains stability, can only be seen in ICB non-responders (Sade-Feldman et al., 2017). Epigenetically, tumor cells can regulate HLA-I gene expression through their promotor hypermethylation. This always leads to the inactivation of HLA-A, HLA-B, and HLA-C transcription (Ye et al., 2010). Histone methyltransferase Ezh2 can be upregulated by intratumoral T cells and TNF-α in melanoma; then, it promotes the loss of Immunogenicity and silences antigen presentation to result in immunotherapy-induced immune resistance in melanoma (Zingg et al., 2017).

Environment also matters—it was reported that exposure to ultraviolet radiation and/or cigarette smoke can increase TMB and secondarily neoantigen levels, which may increase the response rate to ICB in melanoma and NSCLC, respectively (Morad, et al., 2021). Environment is related to more things we are exposed to, such as sociological factors, lifestyle (diet, physical exercise, smoking, and alcohol consumption), and climate. More studies are needed to draw conclusions about the influences of these factors on ICB response. However, our studies ignore the influences of the environment on ICB resistance, instead focusing on the genetic factors.

5.2 IrAEs

Despite boosting antitumor immunity, an immune systems that is excessively activated by ICBs also introduces the development of irAEs, which range from skin pruritus to fatal events. The mechanisms of irAEs differ between various ICIs, and the precise mechanisms remain to be explored. But the main mechanisms are as follows: The use of ICIs can activate T cells, impairing Treg to increase the ratio of effector T cells in the TME. It also can increase the production of pro-inflammatory cytokines such as TNF, IFN-γ, and IL-2, which always

leads to colitis (Sullivan and Weber, 2022). Cross-reactivity between anti-tumor T cells and similar antigens on healthy cells might account for some irAEs, such as myocarditis (Johnson et al., 2016). Activated T cells mediated by ICIs can interact with B cells to produce autoantibodies. This usually happens in patients treated with CTLA-4 antibody but not with PD-1 and PD-L1 inhibitors, leading to irAEs such as hypophysitis. Additionally, complement can mediate injury directly from ICB (Sullivan and Weber, 2022).

IrAEs can occur in nearly every organ, including liver, lungs, gastrointestinal and endocrine organs, the heart, and skin (Dolladille et al., 2020). An estimation of 36 phase II/III trials of ICBs showed a frequency of 54% to 76% for all adverse events (Xu et al., 2018). The clinical usage of combination therapy with nivolumab and ipilimumab is also constrained because of the high rate of severe irAEs (Pauken et al., 2019). Usually, grade 1 irAEs, referring to asymptomatic or mild symptoms, can be stopped temporarily or continued with close monitoring, without interventional treatment. However, patients with grade 2 or higher irAEs should stop ICIs and be referred to a specialist. Meanwhile, grade 2 irAEs mean that age-appropriate instrumental activities of daily living (ADL) are limited, and patients should be treated with glucocorticoids, except for endocrine irAEs (Brahmer et al., 2018), and prednisone is usually the first choice. While patients with grade 3 (where the symptoms are severe or medically significant but not immediately life-threatening) or 4 (showing life-threatening consequences) irAEs should be treated with steroids initially, such as starting methylprednisolone pulses (Torino et al., 2016). In addition, hormonal replacement can relieve endocrine irAEs (Sznol et al., 2017). More detailed management guidelines targeting specific organs can be found in other guidelines (Brahmer, et al., 2018). Administering other drugs according to the specific symptoms in order to manage irAEs is necessary for clinical applications (Martins et al., 2019), and the potential predictive biomarkers such as MHC, gut microbiota, and tumor-infiltrating lymphocytes (TILs) need to be improved (Mahadevan et al., 2021; Hone Lopez et al., 2022; Wang et al., 2022). Moreover, ICIs are expensive, and their use can significantly increase costs. The financial burden limits access and may further strain healthcare resources in developing nations (Merchant et al., 2023).

6 Perspective

Immune checkpoint therapy aims to restore the function of tumor-infiltrating T cells. Hot tumors, characterized by high T cell infiltration, respond well to immune checkpoint therapy. In contrast, cold tumors, lacking T-cell infiltration, respond weakly (Chen and Mellman, 2017). Cold tumors are also characterized by low mutational load, low MHC-I expression, low PD-L1 expression, and the presence of immunosuppressive cell populations, including Tregs, TAMs, and MDSCs. Deficiencies in T cell priming and homing to the tumor bed contribute to the weak response. It is critical to find approaches to convert cold tumors to hot for a better response and less resistance to immunotherapy. Key strategies include promoting T cell priming, promoting T cell expansion, and promoting T cell trafficking and infiltration (Liu and Sun, 2021).

Nowadays, many combination strategies have been developed to improve efficacy and overcome ICB resistance. Treatment with DNA methyltransferase inhibitors, individually or combined with Histone deacetylase (HDAC) inhibitor to modulate epigenetic status, promotes antigen presentation (Luo et al., 2018). Other combination treatment strategies are also under investigation. Signal modulators, such as the combination of atezolizumab (anti-PD-L1) and BRAF/MEK inhibitors in melanoma, increase PFS significantly (NCT02908672). PI3K inhibitors and cyclin-dependent kinase (CDK) 4/6 can reverse signal defects (Goel et al., 2017; Marijt et al., 2019). Cytokines like IL-2 or IL-12 can be introduced to increase the abundance of TIL, but usually with severe toxicity because of the systematic pro-inflammatory side effects (Panelli et al., 2004). So, confining cytokines to the site of action may be an effective improvement measure. Anti-angiogenic agents, when combined with ICIs, are proven to expand immune cell infiltration in tumors. For example, bevacizumab (anti-angiogenic agent) combined with atezolimumab (anti-PD-L1) has been approved by the FDA for the treatment of unresectable or metastatic hepatocellular carcinoma (Finn et al., 2020). Vaccines are another approach to increasing T cell infiltration. It has been shown that the CD103 cDC1 vaccine, combined with CTLA-4 antibody, control primary and metastatic melanoma and osteosarcoma in mice (Finn, et al., 2020). Oncolytic viruses (OV) can mediate the lysis of tumor cells directly or make tumor cells release antigen and activate an inflammatory response, thus inducing antitumor immunity response. However, inadequate OV penetration and spread and host antiviral immunity are barriers to be overcome (Ma et al., 2023).

Combining ICB with other strategies, such as adoptive T cell transfer, radiation, chemotherapy, and intra-tumoral therapies, is being actively explored, with the aim of increasing the sensitivity of tumors to immunotherapy (Meric-Bernstam et al., 2021). Furthermore, treatments based on cytokines, such as the therapeutic neutralization of interleukins, recombinant and engineered interleukins, TNF antagonists, and TGF-β inhibition, are also promising targets for the modulation of the immune-related toxicities of other anti-tumor therapies, including ICBs. (Briukhovetska et al., 2021; Propper and Balkwill, 2022). Due to the complexity of tumor types and individual patient differences, developing biomarkers—even biomarker panels to indicate the response and resistance to ICB monotherapy and combinatorial therapies—is crucial for guiding the selection of treatment and optimizing patient outcomes (Ganesan and Mehnert, 2020).

Patient adherence is one of the factors influencing efficacy. The complexity of combination strategies' precise compatibility, the irAEs of drugs, patients' anxiety, and even the loss of monitoring can lead to lower patient adherence. A clinical trial used the web application KidneyPRO to monitor and manage the toxicities of patients undergoing treatment with the new combination of axitinib/pembrolizumab for a renal cell carcinoma in the first line (NCT04764487). The application provided care adapted to irAEs quickly and personally, improving patient adherence and OS. A clinical trial investigated the ePRO follow-up of cancer patients treated with anti-PD-(L)1 therapies. These patients felt that ePRO follow-up was easy to use and improved their cancer care, and the results showed good patient adherence and satisfaction (Iivanainen et al., 2020). In the long run, automated patient health management is poised to revolutionize the follow-up of cancer patients treated with

ICB.

Comparative results showed that immunotherapy monotherapy has a similar efficacy to that of chemotherapy, but the combination of immunotherapy and chemotherapy provided better efficacy, cutting the death rate (Wang et al., 2023). Several studies have demonstrated that ICIs are superior to other anti-cancer therapies (chemotherapy, targeted therapies, other immunotherapy strategies) across various symptoms and in terms of health-related quality of life, despite the high rate of high grade irAEs (Hall et al., 2019). However, the existing patient-reported outcomes (PRO) cannot adequately assess the many toxicities patients experience after ICI therapy; therefore, it is necessary to develop new PRO tools to capture the symptoms of patients treated with ICIs.

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Author contributions

Qingqing WANG and Yin SHI determined the topic of the article and proposed this program. Hongying YE, Weijie LIAO and Jiongli PAN collected the literature and wrote the manuscript. Hongying YE and Weijie LIAO summarized and drew the tables and pictures. Qingqing WANG and Yin SHI reviewed and edited the manuscript.

Compliance with ethics guidelines

Qingqing WANG, Yin SHI, Hongying YE, Weijie LIAO and Jiongli PAN declare no competing interests.

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Table 1. The number of clinical trials on commonly used immune checkpoint inhibitors.

Target	Drug	Cancer Type	Clinical trials no.			
			Phase 1	Phase 2	Phase 3	Phase 4
CTLA-4	Ipilimumab	Non-small Cell Lung Cancer	35	53	16	1
		Small Cell Lung Cancer	10	14	2	0
		Hepatocellular Carcinoma	10	14	4	0
		Melanoma	118	176	22	2
		Breast Cancer	16	20	1	0
		Leukemia	17	6	0	0
		Colorectal Cancer	17	21	4	0
		Prostate Cancer	17	28	3	0
		Gastric Cancer	6	12	3	0
	Tremelimumab	Non-small Cell Lung Cancer	10	16	4	0
		Small Cell Lung Cancer	5	2	3	0
		Hepatocellular Carcinoma	4	14	2	0
		Melanoma	10	8	1	0
		Breast Cancer	9	10	0	0
		Colorectal Cancer	8	10	0	0
		Prostate Cancer	5	7	0	0
		Gastric Cancer	3	4	0	0
	AGEN1884	Advanced Solid Cancers	2	2	0	0
PD-1	Pembrolizumab	Non-small Cell Lung Cancer	174	216	51	3
		Small Cell Lung Cancer	26	27	3	0
		Melanoma	143	163	14	1

		Gastric cancer	50	64	10	0
		Esophageal cancer	33	46	10	0
		Liver cancer	23	45	7	0
		Breast cancer	95	122	9	0
		Renal cell carcinoma	65	54	11	0
		Squamous cell carcinoma of head and neck	86	133	12	1
		Colorectal cancer	71	70	6	0
		Cervical cancer	50	72	12	0
		Merkel cell carcinoma	16	12	3	0
		Lymphoma	68	79	1	0
	Nivolumab	Non-small cell lung cancer	106	151	29	3
		Squamous cell carcinoma of head and neck	41	64	8	0
		Gastric cancer	25	31	9	0
		Esophageal cancer	16	29	6	0
		Small cell lung cancer	18	27	2	0
		Melanoma	116	163	24	2
		Colorectal cancer	47	64	5	0
		Liver cancer	36	52	7	1
		Renal cell carcinoma	61	86	14	4
		Lymphoma	63	75	5	0
	Durvalumab	Non-small cell lung cancer	39	104	28	4
		Small cell lung cancer	9	27	7	0
		Urothelial cell carcinoma	5	11	1	1
	Cemiplimab	Non-small cell lung cancer	4	7	4	0
		Cutaneous Squamous Cell Carcinoma	2	3	0	0
	Camrelizumab	Non-small cell lung cancer	2	17	5	0
		Liver cancer	7	26	9	0
	Sintilimab	Non-small cell lung cancer	9	32	7	0
	Tislelizumab	Non-small cell lung cancer	5	15	9	0
PD-L1	Atezolizumab	Non-small cell lung cancer	40	92	25	2
		Small cell lung cancer	14	31	8	0
		Breast cancer	38	55	16	0
		Urothelial cell carcinoma	11	22	2	0
		Liver cancer	13	30	8	1
	Avelumab	Urothelial cell carcinoma	6	9	0	0
		Renal cell carcinoma	9	11	4	0
		Merkel cell carcinoma	9	13	1	0

Table 2. Incidence of some common all-grades potential immune-related adverse events (irAEs) in advanced melanoma (Almutairi et al., 2020)

irAEs	Ipilimumab	Nivolumab	Pembrolizumab	Ipilimumab + Nivolumab
Rash (%)	20.54	18.10	13.47	30.68
Pruritus (%)	24.88	22.53	21.40	33.73
Vitiligo (%)	2.39	9.13	7.69	8.61
Diarrhoea (%)	27.74	17.68	11.14	35.69
Colitis (%)	6.87	1.88	1.64	11.80
Hypothyroidism (%)	2.05	7.09	8.15	16.37
Hyperthyroidism (%)	0.88	3.17	3.83	10.59
Hypophysitis (%)	2.58	0.31	1.64	10.86
Hepatitis (%)	0.29	3.01	0.68	4.85
Hyperglycemia (%)	0.75	0.58	5.57	2.60
Acute renal injury (%)	0.31	0.04	0.26	0.52

Table 3. Clinical trials on novel immune checkpoint inhibitors

Target	Drug	Clinical trial no.	Phase	Tumor types
B7-H3	DS-7300a	NCT04145622	1,2	Advanced Solid Tumor, Malignant Solid Tumor
	Enoblituzumab	NCT04129320	2,3	Head and Neck Cancer, HNSCC
		NCT04630769	1	Ovarian Cancer, Fallopian Tube Adenocarcinoma, Primary Peritoneal Cavity Cancer
		NCT02923180	2	Prostate Cancer
		NCT02982941	1	Neuroblastoma, Rhabdomyosarcoma, Osteosarcoma, Ewing Sarcoma, Wilms Tumor, Desmoplastic Small Round Cell Tumor
	HS-20093	NCT05276609	1	Advanced Solid Tumor
	MGC018	NCT05293496	1	Advanced Solid Tumor, Castration-Resistant Prostatic Cancer, Malignant Melanoma, Pancreatic Ductal Carcinoma, Hepatocellular Cancer, Epithelial Ovarian Cancer, RCC
		NCT03729596	1,2	Squamous Cell Carcinoma of Head and Neck, Triple Negative Breast Cancer, Melanoma, Advanced Solid Tumor, Adult, Metastatic Castrate Resistant Prostate Cancer, Non Small Cell Lung Cancer
	MGA271	NCT01918930	1	Melanoma
	MGD009| MGA012	NCT03406949	1	Advanced Solid Tumors
	MGD009	NCT02628535	1	Mesothelioma, Bladder Cancer, Melanoma, Squamous Cell Carcinoma of the Head and Neck, Non Small Cell Lung Cancer, Clear Cell RCC, Ovarian Cancer, Thyroid Cancer, Breast Cancer, Pancreatic Cancer, Prostate Cancer, Colon Cancer, Soft Tissue Sarcoma
	4SCAR-276	NCT04432649	1,2	Solid Tumor
	131I-8H9	NCT01099644	1	Peritoneal Cancer
		NCT00089245	1	Brain and Central Nervous, System Tumors, Neuroblastoma, Sarcoma
		NCT03275402	2,3	Neuroblastoma, Central Nervous System Metastases, Leptomeningeal Metastases
B7-H4	PF-07260437	NCT05067972	1	Ovarian Neoplasms, Endometrial Neoplasms, Breast Neoplasms
	SGN-B7H4V	NCT05194072	1	Ovarian Neoplasms, Peritoneal Neoplasms, Fallopian Tube Neoplasms, Triple Negative Breast Neoplasms, HER2 Negative Breast Neoplasms, Hormone Receptor Positive Breast Neoplasms, Endometrial Neoplasms Carcinoma, Non-Small-Cell Lung Cholangiocarcinoma, Gallbladder Carcinoma
	FPA150| Pembrolizumab	NCT03514121	Early Phase 1	Breast Cancer, Ovarian Cancer, Endometrial Cancer, Advanced Solid Tumors
	HS-20089	NCT05263479	1	Advanced Solid Tumor
	GEN1047	NCT05180474	1,2	Breast Cancer, Uterine Cancer, Ovarian Cancer, NSCLC, Cervical Cancer, Head and Neck Squamous Cell Carcinoma, Except for Nasopharyngeal

				Carcinoma, Urothelial Cancer, Cholangiocarcinoma
	NC762	NCT04875806	1,2	Advanced or Metastatic Solid Tumors, Ovarian Cancer, NSCLC, Breast Cancer
VISTA	CA-170	NCT02671955	1	Advanced Cancer
	JNJ-61610588	NCT02812875	1	Advanced Solid Tumors or Lymphomas
	CI-8993	NCT04475523	1	Solid Tumor
TIM3	Sabatolimab (MGB453)	NCT04812548	2	MDS
		NCT04623216	1,2	AML
		NCT04878432	2	MDS
		NCT05367401	1,2	MDS, AML
		NCT05201066	2	MDS, Leukemia, Myelomonocytic, Chronic
		NCT04097821	1,2	Myelofibrosis
		NCT04150029	2	AML
		NCT03946670	2	MDS
		NCT04266301	3	MDS, Leukemia, Myelomonocytic, Chronic
	Cobolimab (TSR-022)	NCT03680508	2	Adult Primary Liver Cancer, Advanced Adult Primary Liver Cancer, Localized Unresectable Adult Primary Liver Cancer
		NCT04139902	2	Melanoma Stage III,Melanoma Stage IV
		NCT02817633	1	Neoplasms
		NCT03307785	1	Neoplasms, Metastatic Cancer, Advanced Cancer, Solid Tumor, NSCLC Metastatic, NSCLC Stage IIIB, NSCLC
	Sym023	NCT03489343	1	Metastatic Cancer, Solid Tumor, Lymphoma
		NCT04641871	1	Metastatic Cancer, Solid Tumor
		NCT03311412	1	Metastatic Cancer, Solid Tumor, Lymphoma
	BGBA425	NCT03744468	1,2	Locally Advanced or Metastatic Solid Tumors for Phase 1 HNSCC, NSCLC and RCC for Phase 2
	LY3321367	NCT03099109	1	Solid Tumor
		NCT02791334	1	Solid Tumor, Microsatellite Instability-High (MSI-H) Solid Tumors, Cutaneous Melanoma, Pancreatic Cancer, Breast Cancer (HR+HER2-)
	BMS-986258	NCT03446040	1,2	Advanced Cancer
	SHR-1702	NCT04443751	1	AML, MDS
		NCT03871855	1	Advanced Solid Tumor
LAG-3	Eftilagimod Alpha (IMP32)	NCT03625323	2	NSCLC, HNSCC
		NCT04811027	2	HNSCC
		NCT02676869	1	Stage IV Melanoma, Stage III Melanoma
		NCT04252768	1	Metastatic Breast Cancer
		NCT02614833	2	Adenocarcinoma Breast Stage IV
		NCT03600090	1	Solid Tumor, Adult
	Relatlimab (BMS-936558)	NCT03743766	2	Melanoma
		NCT04552223	2	Metastatic Uveal Melanoma
		NCT02061761	1,2	Hematologic Neoplasms
		NCT03623854	2	Chordoma, Locally Advanced Chordoma, Metastatic Chordoma, Unresectable Chordoma
		NCT01968109	1,2	Neoplasms by Site
	Cemiplimab (REGN3767)	NCT04566978	1	Large B-cell Lymphoma, DLBCL

		NCT03005782	1	Malignancies
		NCT04706715	1,2	Metastatic Solid Tumor
		NCT05352672	3	Melanoma
	BI 754111	NCT03780725	1	Carcinoma, NSCLC, Head and Neck Neoplasms
		NCT03156114	1	Neoplasms, Carcinoma, NSCLC
		NCT03433898	1	Neoplasms
		NCT03964233	1	Neoplasms
	Sym022	NCT03489369	1	Metastatic Cancer, Solid Tumor, Lymphoma
		NCT04641871	1	Metastatic Cancer, Solid Tumor
		NCT03311412	1	Metastatic Cancer, Solid Tumor, Lymphoma
	MGD013	NCT04212221	1,2	Advanced HCC
		NCT04653038	1	Unresectable, Recurrent or Metastatic Melanoma, Untreated Mucosal or Acral Lentiginous Melanoma
		NCT04178460	1	Gastric Cancer, Triple Negative Breast Cancer, Biliary Tract Carcinoma, Endometrial Carcinoma
		NCT04129320	2,3	Head and Neck Cancer, HNSCC
	Favezelimab (MK-4280)	NCT03598608	1,2	Hodgkin Disease, Lymphoma (Non-Hodgkin), Lymphoma (B-Cell)
		NCT05064059	3	Colorectal Cancer
		NCT02720068	1	Neoplasms
	TSR-033	NCT03250832	1	Neoplasms
TIGIT	Tiragolumab	NCT05251948	1,2	Gastric and Gastroesophageal Junction Carcinoma
		NCT03563716	2	NSCLC
		NCT03708224	2	Squamous Cell Carcinoma, Head and Neck Cancer
		NCT04933227	2	Stomach Neoplasms, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma
		NCT05009069	2	Rectal Neoplasms, Rectal Cancer
		NCT04543617	3	Esophageal Squamous Cell Carcinoma
		NCT04256421	3	Small Cell Lung Cancer
		NCT04294810	3	NSCLC
	JS006	NCT05061628	1	Advanced Tumors
	IBI939	NCT04353830	1	Advanced Malignant Tumors
		NCT04672369	1	Advanced Lung Cancer
	BMS-986207	NCT04150965	1,2	Relapsed/Refractory MM
		NCT04570839	1,2	Endometrial Neoplasms, Ovarian Cancer, Solid Tumor, Head and Neck Cancer
	Etigilimab (MP-313M32）	NCT03119428	1	Locally Advanced Cancer, Metastatic Cancer
		NCT04761198	1,2	Advanced Solid Tumor, Metastatic Solid Tumor
	COM902	NCT04354246	1	Advanced Cancer, Ovarian Cancer, Lung Cancer, Colon Cancer, Plasma Cell Neoplasm, MM, HNSCC
	AZD2936	NCT04995523	1,2	NSCLC
	Ociperlimab	NCT04047862	1	Locally Advanced and Metastatic Solid Tumors
		NCT04693234	2	Cervical Cancer
		NCT04732494	2	Esophageal Squamous Cell Carcinoma
		NCT04952597	2	Limited Stage Small Cell Lung Cancer
		NCT04866017	3	NSCLC
	HLX301	NCT05102214	1,2	Locally Advanced or Metastatic Solid Tumors, NSCLC
		NCT05390528	1,2	Advanced Tumors, Lymphoma,

				Metastatic Tumors
	M6223	NCT04457778	1	Metastatic Solid Tumors
		NCT05327530	2	Locally Advanced or Metastatic Urothelial Carcinoma
	BAT6021	NCT05120375	1	Solid Tumor
		NCT05073484	1	Advanced Solid Tumor
	Domvanalimab	NCT03628677	1	Solid Tumor
		NCT05130177	2	Melanoma
		NCT05329766	2	Gastrointestinal Tract Malignancies
		NCT04791839	2	Non-small Cell Carcinoma
		NCT04262856	2	NSCLC, Nonsquamous NSCLC, Squamous NSCLC,
		NCT04736173	3	NSCLC, Nonsquamous NSCLC, Squamous NSCLC
	EOS-448	NCT05060432	1,2	Advanced Cancer, Lung Cancer, Head and Neck Cancer, Melanoma
		NCT05289492	1,2	Relapsed/Refractory MM
		NCT03739710	2	Neoplasms
BTLA	JS004	NCT04278859	1	Advanced Solid Tumor
		NCT04137900	1	Advanced Unresectable Solid Tumor, Metastatic Solid Tumor
		NCT04929080	1,2	HNSCC, Nasopharyngeal Carcinoma
		NCT04773951	1	Melanoma, Renal Carcinoma, Urothelial Carcinoma
		NCT04477772	1	Recurrent/Refractory Malignant Lymphoma
		NCT05000684	1,2	Advanced Lung Cancer

HNSCC, head and neck squamous cell carcinoma; RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; MM, multiple myeloma; DLBCL, diffuse large B cell lymphoma; HCC, hepatocellular carcinoma

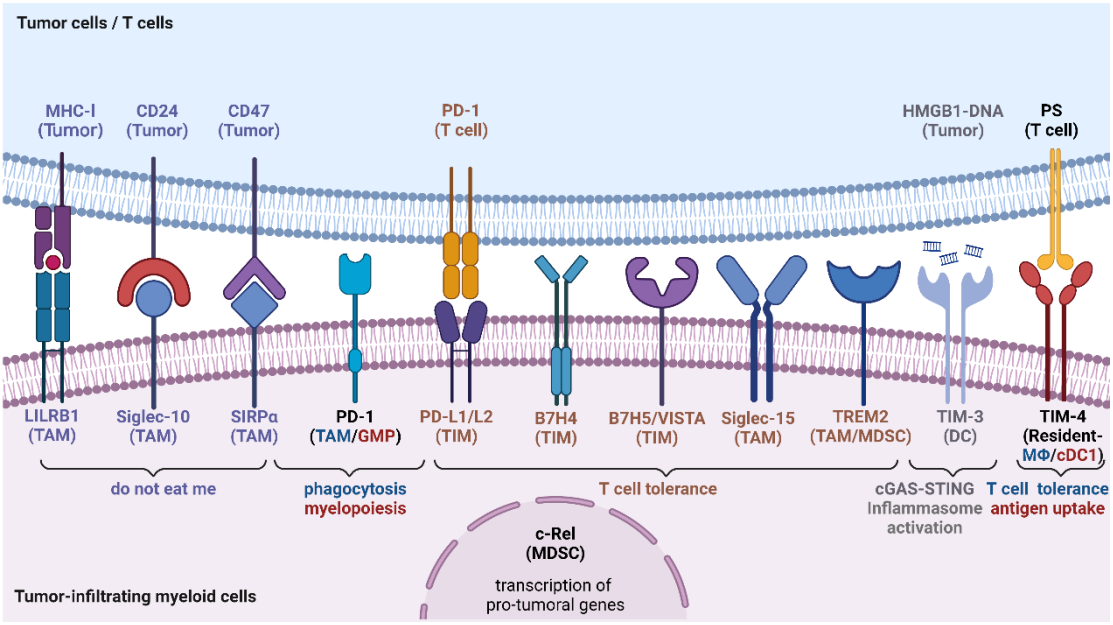

Figure 1. Immune checkpoints on tumor-infiltrating myeloid cells.

Immune checkpoints in tumor-infiltrating myeloid cells have a variety of functions, which encompass the activation of the "do not eat me" signal, phagocytosis, myelopoiesis, T cell tolerance, inflammasome activation, antigen uptake, and transcription of pro-tumoral genes. Abbreviation: MHC-I, major histocompatibility complex-I; PD-1, programmed cell death-1; HMGB1, high mobility group protein 1; PS, phosphatidylserine; LILRB1, leukocyte immunoglobulin-like receptor B1; SIRPα, signal regulatory protein α; PD-L1/L2, programmed death-ligand 1/2; VISTA, V-domain Ig suppressor of T-cell activation; TREM2, triggering receptor expressed on myeloid cells 2; TIM-3/4, T cell immunoglobulin and mucin domain-containing protein 3/4; TAM, tumor associated macrophage; GMP, granulocyte-monocyte progenitor; TIM, tumor infiltrating macrophage; MDSC, myeloid-derived suppressor cells; DC, dendritic cell; Mϕ, macrophage; cDC1, conventional dendritic cell 1.